DEPARTMENT OF HEALTH & HUMAN SERVICES

94514

Public Health Service
Food and Drug Administration
Los Angeles District

19701 Fairchild
Irvine, California 92612-2506
Telephone (949) 608-2900

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

January 27, 2004 W/L 22-04

Mr. Paul L. Woodring,
President
Respironics, California, Inc.
2271 Cosmos Court
Carlsbad, CA 92009

Dear Mr. Woodring:

An investigator from the Food and Drug Administration (FDA) conducted an inspection of your firm located in Carlsbad, California from May 29 to June 27, 2003. Your firm manufactures the "Esprit" microprocessor-controlled, electrically-powered mechanical ventilator, which is intended to provide continuous or intermittent ventilator support for adult and pediatric patients as prescribed by a physician. This ventilator is a device as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h).

Our inspection disclosed that your Esprit ventilator device is adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation do not conform with the Good Manufacturing Practice (GMP) requirements set forth in the Quality System Regulation, Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. The design validation activities conducted for the Esprit ventilator software version 3.2 failed to ensure that the device conforms to the defined user/patient needs and intended uses [21 CFR 820.30]. Specifically:

   - There was no documented evidence that any integration and throughput testing of the device was performed to eliminate software communication problems prior to the final acceptance of the design of the device.

- Your design review procedures were not properly defined to ensure that the participants at each design review included proper representatives of all functions concerned with design stage. Our investigator was advised that the decision to conduct integration and throughput testing rested with management only.

- There was no risk assessments performed to ensure that any changes made in the device to eliminate or minimize any hazards associated with torn and separated check valves did not introduce any new hazards or adversely affect the device.

- Design verification did not confirm that the design output meets the design input requirements. Specifically, design verification and validation activities associated with the changes in the check valves to eliminate and minimize torn and separated check valves was only conducted on an exhalation check valve and no such activities were conducted on the inspiration check valves.

2. The Esprit Throughput Testing Package, a written software test procedure for the throughput testing that is used in conducting software integration testing, was found in use even though it had not been released, controlled, or approved in accordance with written document control procedures [21 CFR 820.40(a)].

3. Procedures for the control of manufacturing and storage areas where environmental conditions could be reasonably expected to have an adverse effect on product quality were not adequately followed [21 CFR 820.70(c)]. Specifically, preventive maintenance of the Electrostatic Discharge (ESD) grounding systems installed in the ESD workstations was not conducted in accordance with all established procedures and specified intervals. Printed Circuit Boards Assemblies (PCBA) identified as ESD sensitive components were observed in opened ESD protective packaging in unprotected metal storage and transfer carts. Relative Humidity readings of 19% and 20% -- which fall below your specified [redacted]% to [redacted]% limits -- were disclosed in your failure investigations work area in February and March 2003 without any documented evidence to ensure that any electrostatic-sensitive components were not handled in those areas as described in your established written procedures.

4. Potential suppliers of components were not sufficiently evaluated and selected on the basis of their ability to meet specified requirements [21 CFR 820.50(a)(1)]. Specifically, the selection and qualification of your supplier of flow sensors used in the production of the Esprit failed to ensure that the supplier had established all of the proper fabrication features and procedures for the dielectric coating and substrate used in the plating and sputtering process necessary to assure that all of the specified design characteristics, dimensions, design, materials and performance were met, and to prevent the flow sensors from having calibration drifts. Calibration drifts detected in the flow sensors received from this supplier resulted in field correction activities in 2002 and 2003.

5. Procedures addressing the implementation and recording of changes in methods and procedures needed to correct and prevent identified quality problems were not complete [21 CFR 820.100(a)(5)]. Specifically, your written corrective and preventive procedures failed to ensure that the corrective action associated with a health risk was completed in a timely manner. A field communication was issued on 6/8/01 to replace some check valves that presented a health risk from tearing and separation. Our investigation disclosed that some of these valves were not replaced for many months without any written justification for the delay.

Additionally, the Esprit ventilator is misbranded within the meaning of Section 502(t)(2) of the Act (21 U.S.C. 352(t)(2)) because your firm failed to furnish certain information to FDA as required by FDA regulations at 21 CFR Part 803 (Medical Device Reporting) and 21 CFR Part 806 (Reports of Corrections and Removals). These regulations implement certain provisions of section 519 of the Act.

The Esprit ventilator is misbranded within the meaning of Section 502(t)(2) of the Act because your firm failed to submit information to the FDA as required by the Medical Device Reporting (MDR) regulations set forth at 21 CFR Part 803. Specifically, your firm failed to submit two (2) Malfunction MDRs involving defective check valves that were tearing and separating (MDR # 2031642-2003-0003 and MDR # 2031642-2003-00004) within thirty (30) days after your firm received the information regarding the associated complaints, as required by 21 CFR 803.50(a)(2). In fact, it took your firm over 2 years after it became aware of the associated complaints to submit these two Malfunction MDRs.

With respect to the two above-referenced Malfunction MDRs, one incident involved a patient on the ventilator who was not receiving mandatory breaths or tidal volume due to a check valve leak, and the other incident, although it did not involve a ventilator in use on a patient, involved a ventilator that failed an extended self test, later determined to be due to a check valve leak. Both of these incidents were reportable [21 CFR 820.50(a)(2)]. As your firm's own MDR procedures acknowledge, a malfunction should be considered reportable if "it causes the device to fail to perform its essential function and compromises the device's therapeutic, monitoring or diagnostic effectiveness which could cause or contribute to a death or serious injury, or other significant adverse device experiences." With respect to the malfunctions at issue, the defective check valves tore off and blocked air from entering the inspiration manifold or from exiting the exhalation assembly. These malfunctions prevented, or could prevent, the flow of air to and from the patient, and compromised, or could compromise, the device's therapeutic effectiveness, which could cause or contribute to a death or serious injury. The malfunctions were therefore reportable. [21 CFR 820.50(a)(2); 21 CFR 803.3(n); 21 CFR 803.3(r)(2)(ii)].

We find insufficient the justification provided in your June 25, 2003 letter as to why your firm failed to submit MDR # 2031642-2003-00003 and MDR # 2031642-2003-00004 in a timely fashion. Your firm stated that when the underlying complaints were received,

they were not determined to be reportable, and it was not until your firm received two additional complaints that it reported as Serious Injury MDRs that your firm re-reviewed the reportability of the two malfunction complaints. However, based on our review of your records, your firm became aware of the first of the Serious Injury MDRs on 5/31/01, several days before it became aware of the malfunction complaints on 6/4/01 and 6/8/01, respectively. Therefore, your firm should have known that if the malfunctions were to recur, they would be likely to cause or contribute to death or "serious injury," and thus were MDR reportable events, as required by 803.50(a)(2).

The Esprit Ventilator is further misbranded within the meaning of Section 502(t)(2) of the Act because your firm failed to furnish reports of corrections and removals as required by 21 CFR Part 806. Specifically, your firm failed to submit written reports to FDA within 10 working days of initiating field corrections to reduce a "risk to health" posed by the device [21 CFR 806.10(a), (b)]. These field corrections were undertaken to eliminate problems associated with torn and separated check valves for the Esprit ventilator (i.e., Field Communication Notice 2001-25 dated June 8, 2001), and to eliminate CBIT task starvation causing watchdog timeout (INOP 8001 diagnostic code) involving a throughput problem, as a result of which the Esprit ventilator unexpectedly shut down and restarted within thirty (30) seconds (i.e., effectively included in part of Field Communication Notice 2001-23 dated June 1, 2001). It took almost two (2) years for your firm to submit a report concerning corrections made to the Esprit Ventilator check valves, and no report was submitted concerning the corrections made to eliminate the CBIT task starvation problem.

The FDA conducted Health Hazard Evaluations (HHEs) on the problems associated with the torn and separated check valves, as well as on the problems associated with the CBIT task starvation. FDA determined that with regard to the torn and separated check valves there was a "risk to health" within the meaning of 21 CFR 806.2(j)(1), in that there was a reasonable probability that use of, or exposure to, the product would cause serious adverse health consequences or death. FDA further determined that with regard to the CBIT starvation problem there was a "risk to health" within the meaning of 21 CFR 806.2(j)(2), in that the use of, or exposure to, the product with this problem could cause temporary adverse health consequences. Because there was a risk to health, the corrections initiated by your firm to reduce this risk should have been reported to FDA on a timely basis as required by 21 CFR 806.10(b).

The reason your firm provided in its June 25, 2003 letter as to why it did not submit a correction or removal report for its correction of the torn and separated check valves does not adequately justify your failure to submit a timely report. Your firm stated that it performed a Heath Hazard Analysis on this problem after receipt of the first Serious Injury MDR report, and based on your information at the time, you determined that the malfunction "was not likely to cause adverse health consequences."

However, based on our review, it appears that your firm did at that time have evidence that the malfunction met the definition of "risk to health" under 21 CFR 806.2(j)(2), i.e. "[t]hat use of ... the product may cause temporary or medically reversible adverse health

consequences...." According to your firm's June 13, 2001 Health Hazard Analysis, the first Serious Injury MDR involved a patient cyanotic (turned blue) who was removed from the ventilator, manually bagged until stable, and then placed on another ventilator. This was evidence that your product with this malfunction could cause temporary or medically reversible adverse health consequences. In fact, you submitted the first MDR as a "Serious Injury" MDR. Such a "serious injury" is by definition an injury that is life threatening, results in permanent impairment of a body function or permanent damage to a body structure, or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure (21 CFR 803.3(bb)).

Moreover, your firm performed a correction or removal of a device to reduce a risk to health posed by the product. The Health Hazard Analysis indicates that your firm received at least twelve complaints of check valve failures (SV2), four of which involved blockages, and three of which occurred on patients. Your firm subsequently submitted an additional "Serious Injury" MDR in which the patient appeared to be in respiratory distress and was diaphoretic, and was stabilized after being removed from the ventilator. Your firm's investigation determined that the material hardness of the check valve made it subject to tearing after 2800 hours of operation (premature failure), and there was a problem with its orientation which subjected it to undue stress on its "hinged" area. After changing the hardness of the check valve to improve durability and changing its orientation, your firm had service representatives replace the check valves in all distributed devices with the new check valves/new orientation via the referenced Field Communication 20001-25. Having performed this correction or removal, your firm should have been aware of the need to report it to FDA under 21 CFR 806.10 (a)(1).

We have also reviewed your firm's July 29, 2003 letter. We believe that item 6.2.3 on page 9 of the Adverse Event Reporting document included with that letter could be confusing, does not accurately reflect the definition of a MDR Serious Injury, and could result in unreported serious injuries. Also, all references in your letter and attached documents to distributor MDR reporting requirements should be deleted and replaced with the distributor complaint file requirements of 21 CFR 803.18(d) (1), (2), & (3), because the former requirement was revoked by Section 213(a) of the Food and Drug Administration Modernization Act [65 Federal Register 4112, 4113 (Jan. 26, 2000)].

Given the facts provided in this letter, we believe a regulatory meeting between your firm and FDA is warranted to discuss the corrective and preventative actions taken since the completion of our inspection.

We have identified the following concerns that we wish to discuss with you at the meeting:

- Design procedures and design history for the Esprit ventilator, especially software changes made to the device;

- Procedures for handling of all written and oral complaints;

- Procedures for conducting internal and external audits;

- Procedures for reviewing and conducting investigations of products that do not conform to their specified requirements; and

- Procedures for submitting required reports to the FDA such as MDRs, corrections and removals, and recalls.

Please contact FDA Senior Compliance Officer Dannie E. Rowland at (949) 608-4448 in order to make necessary arrangements for the meeting, or if you have any questions.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each applicable requirement of the Act and regulations. The specific violations noted in this letter and in the Form FDA 483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance system. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal Agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no applications for premarket approval of Class III devices to which Quality System regulation deficiencies are reasonably related will be approved until the violations have been corrected. Also, no request for Certificates to Foreign Governments will be granted until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration against you or your product without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not occur in the future. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which you believe the corrections will be completed. You may elect to bring your written response to this letter to the meeting in lieu of mailing it to our office.

If you decide to submit your response by mail, please send it to:

Acting Director, Compliance Branch
Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2445

Sincerely,

Alonza E. Cruse
District Director
Los Angeles District Office

Cc: State Department of Public Health
Environmental Health Services
Attn: Chief, Food and Drug Branch
601 North 7th Street, MS-35
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Cc: James Liken
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